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(54) Title: COMPOUNDS			
<p style="text-align: center;">(I)</p>			
<p style="text-align: center;">---Ar (a) $\text{---Ar}^1\text{---Y---Ar}^2$ (b)</p>			
<p style="text-align: center;">$\text{---}\text{Ar}$ (c) $(\text{CH}_2)_p\text{---V---}(\text{CH}_2)_q\text{Ar}$ (d)</p>			
(57) Abstract			
<p>Compounds of formula (I) wherein: R¹ represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁₋₄alkyl, C₁₋₄alkoxy, arylC₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkoxyC₁₋₄alkyl, C₃₋₆cycloalkylC₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfonyloxy, C₁₋₄alkylsulfonylC₁₋₄alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₄alkyl, C₁₋₄alkylsulfonamido, C₁₋₄alkylamido, C₁₋₄alkylsulfonamidoC₁₋₄alkyl, C₁₋₄alkylamidoC₁₋₄alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁₋₄alkyl, arylcarboxamidoC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, or arylC₁₋₄alkanoyl group; a group R⁵OCO(CH₂)_p, R⁵CON(R⁶)(CH₂)_p, R⁵R⁶NCO(CH₂)_p or R⁵R⁶NSO₂(CH₂)_p, where each of R⁵ and R⁶ independently represents a hydrogen atom or a C₁₋₄alkyl group or R⁵R⁶ forms part of a C₃₋₆azacycloalkane or C₃₋₆(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar³-Z, wherein Ar³ represents an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring and Z represents a bond, O, S, or CH₂; R² represents a hydrogen atom or a C₁₋₄alkyl group; R³ and R⁴ each independently represent a C₁₋₄alkyl group, q is 1 or 2; A represents a group of the formula (a), (b), (c) or (d).</p>			

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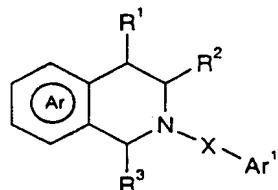
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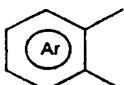
ISOQUINOLINE DERIVATIVES

The present invention relates to novel tetrahydroisoquinoline derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, as modulators of dopamine D₃ receptors, in particular as antipsychotic agents.

US Patent No. 5,294,621 describes tetrahydropyridine derivatives of the formula:

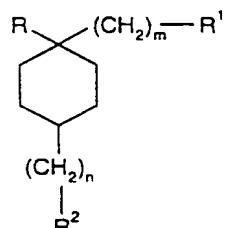


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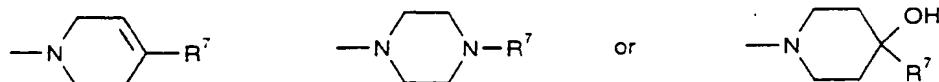


wherein is an optionally substituted thienyl or optionally substituted phenyl ring; R¹, R² and R³ are each *inter alia* hydrogen; X is *inter alia* (CH₂)_mNR⁷CO; m is 2-4; and Ar¹ is an optionally substituted heterocyclic ring or an optionally substituted phenyl ring. The compounds are said to be useful as antiarrhythmic agents.

15 EPA 431,580 describes compounds of formula



20 wherein R is OR³, NR⁴R⁵, or N(OR⁴)R⁵; R⁴ and R⁵ are *inter alia* hydrogen, lower alkyl, aroyl or heteroaroyl; m is zero, 1 or 2; R¹ is hydrogen, aryl or various heteroaryl groups; n is zero or 1-4; and R² is:



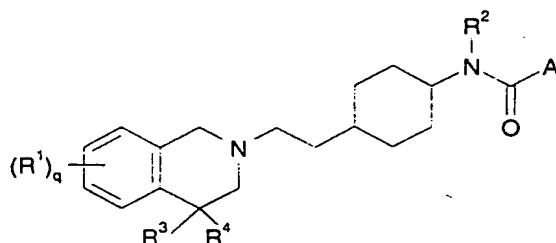
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The compounds are said to be dopaminergic agents useful as antipsychotics, antihypertensives and also of use in the treatment of hyperprolactinaemia-related conditions and several central nervous system disorders.

WO 95/10513 describes benzothiophene derivatives and related compounds as estrogen agonists.

We have now found a class of tetrahydroisoquinoline derivatives which have affinity for dopamine receptors, in particular the D₃ receptor, and thus potential in the treatment of conditions wherein modulation of the D₃ receptor is beneficial, eg as antipsychotic agents.

In a first aspect the present invention provides compounds of formula (I) :



Formula (I)

10 wherein:

R¹ represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁-4alkyl, C₁-4alkoxy, arylC₁-4alkoxy, C₁-4alkylthio,

C₁-4alkoxyC₁-4alkyl, C₃-6cycloalkylC₁-4alkoxy, C₁-4alkanoyl, C₁-4alkoxycarbonyl,

15 C₁-4alkylsulfonyl, C₁-4alkylsulfonyloxy, C₁-4alkylsulfonylC₁-4alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁-4alkyl, C₁-4alkylsulfonamido, C₁-4alkylamido,

C₁-4alkylsulfonamidoC₁-4alkyl, C₁-4alkylamidoC₁-4alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁-4alkyl, arylcarboxamidoC₁-4alkyl, aroyl, aroylC₁-

4alkyl, or arylC₁-4alkanoyl group; a group R⁵OCO(CH₂)_p, R⁵CON(R⁶)(CH₂)_p,

20 R⁵R⁶NCO(CH₂)_p or R⁵R⁶NSO₂(CH₂)_p where each of R⁵ and R⁶ independently represents a hydrogen atom or a C₁-4alkyl group or R⁵R⁶ forms part of a C₃-6azacycloalkane or C₃-6(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar³-Z, wherein Ar³ represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S , or CH₂:

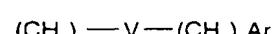
25 R² represents a hydrogen atom or a C₁-4alkyl group;

R³ and R⁴ each independently represent a C₁-4 alkyl group;

q is 1 or 2;

A represents a group of the formula (a), (b), (c) or (d):

30



(a)

(b)

(c)

(d)

wherein

Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system:

5 Ar¹ and Ar² each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; and

Y represents a bond, -NHCO-, -CONH-, -CH₂-, or -(CH₂)_mY¹(CH₂)_n-, wherein Y¹ represents O, S, SO₂, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a 10 methoxy group;

r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4;

V represents a bond, O or S;
and salts thereof.

15 In the compounds of formula (I) above an alkyl group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, and the like.

20 When R¹ represents an arylC₁₋₄alkoxy, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₄alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁₋₄alkyl, arylcarboxamidoC₁₋₄alkyl, aroyl, aroylC₁₋₄alkyl, or arylC₁₋₄alkanoyl group, the aryl moiety may be selected from an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring. In the group R¹ an aryl moiety may be optionally substituted by one or more substituents selected from hydrogen, halogen, 25 amino, cyano, C₁₋₄alkyl, C₁₋₄alkylamino, C₁₋₄dialkylamino, C₁₋₄alkylamido, C₁₋₄alkanoyl, or R⁷R⁸NCO where each of R⁷ and R⁸ independently represents a hydrogen atom or C₁₋₄alkyl group.

A halogen atom present in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine.

30 When q is 2, the substituents R¹ may be the same or different.

An optionally substituted 5- or 6-membered heterocyclic aromatic ring, as defined for any of the groups Ar, Ar¹, Ar² or Ar³ may contain from 1 to 4 heteroatoms selected from O, N or S. When the ring contains 2-4 heteroatoms, one is preferably selected from O, N and S and the remaining heteroatoms are preferably N. Examples of 5 and 6-membered heterocyclic groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl and pyrazolyl.

35 Examples of bicyclic, for example bicyclic aromatic or heteroaromatic, ring systems for Ar include naphthyl, indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, pyrrolo[3,2-c]pyridyl, thieno[3,2-b]thiophenyl, 1,2-

dihydro-2-oxo-quinolinyl, 2,3-dihydro-3-oxo-4H-benzoxazinyl, 1,2-dihydro-2-oxo-3H-indolyl.

The rings Ar, Ar¹, or Ar² may each independently be optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, or a hydroxy, oxo, cyano, nitro, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylenedioxy, C₁₋₄alkanoyl, C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfinyl, C₁₋₄alkylthio, R⁹SO₂N(R¹⁰)-, R⁹R¹⁰NSO₂-, R⁹R¹⁰N-, R⁹R¹⁰NCO-, or R⁹CON(R¹⁰)- group wherein each of R⁹ and R¹⁰ independently represents a hydrogen atom or a C₁₋₄ alkyl group, or R⁹R¹⁰ together form a C₃₋₆ alkylene chain.

10 Alternatively, Ar and Ar² may be optionally substituted by one or more 5- or 6-membered heterocyclic rings, as defined above, optionally substituted by a C₁₋₂ alkyl or R⁹R¹⁰N- group; wherein R⁹ and R¹⁰ are as defined above.

In the rings Ar and Ar² substituents positioned *ortho* to one another may be linked to form a 5- or 6- membered ring.

15 It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids eg. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids eg. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, 20 methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts eg. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

25 Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

30 The compounds of formula (I) can exist in the form of *cis*- and *trans*- isomers with respect to the configuration at the cyclohexyl ring. When A represents a group (c) the compounds may also exist as geometric isomers around the double bond. The present invention includes within its scope all such isomers, including mixtures. Preferably the compounds of the invention are in the *trans* configuration with respect to the cyclohexyl ring. For compounds of formula (I) where A represents a group (c), *trans* geometry of the double bond is preferred.

35 In compounds of formula (I), it is preferred that R¹ represents a substituent selected from: a hydrogen or halogen atom, methyl, cyano, trifluoromethyl, pentafluoroethyl, or trifluoromethoxy group. A cyano group, for example in the 6- or 7-position of the tetrahydroisoquinoline ring, is especially preferred. Preferably q is 1. R² is preferably a hydrogen atom. R³ and R⁴ are preferably methyl groups.

40 The group A is preferably a group of formula (a) or (c). With regard to (a), preferred examples of Ar include optionally substituted indolyl, pyrazolo[1,5-a]pyrimidyl, cinnolinyl, quinolinyl, benzo[b]furanyl or pyrrolopyridyl. With regard to (c), preferred examples are optionally substituted phenyl groups.

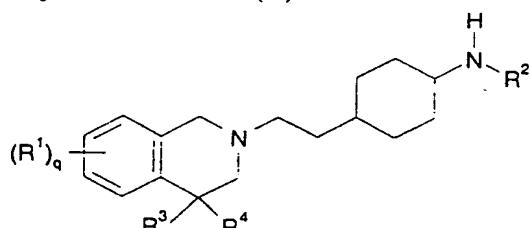
It is also preferred that the rings Ar, Ar¹, or Ar² are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

5 Certain of the substituted heteroaromatic ring systems included in compounds of formula (I) may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

10 Particular compounds according to the invention include those specifically exemplified and named hereinafter. These compounds may be in the form of their free base or physiologically acceptable salts thereof, particularly the monohydrochloride or monomesylate salts.

The present invention also provides a process for preparing compounds of formula (I) which process comprises :

15 (a) reacting a compound of formula (II):



Formula (II)

20 wherein R¹, R², R³, R⁴ and q are as hereinbefore defined, with a compound of formula (III):

A-COX

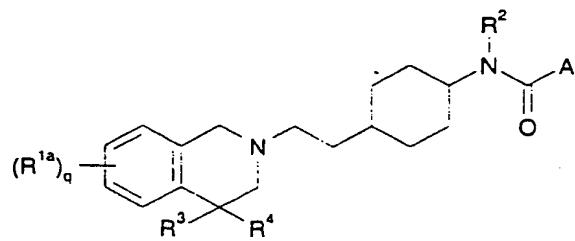
Formula (III)

25

wherein A is as hereinbefore defined and X is a halogen atom or the residue of an activated ester;

(b) to prepare a compound of formula (I) by reacting a compound of formula (II) with a compound A-Br, or A-I, or A-OSO₂CF₃ in the presence of carbon monoxide and a catalyst such as *trans*-bis-triphenylphosphinepalladium(II)bromide;

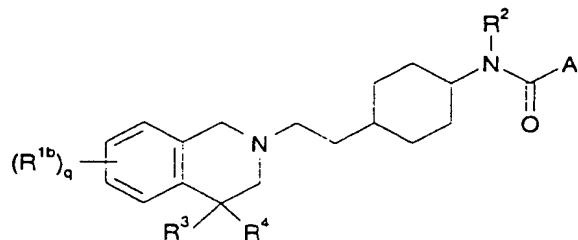
(c) to prepare a compound of formula (I) wherein R¹ is Ar³-Z and Z is a bond, reacting a compound of formula (IV):



Formula (IV)

5 wherein R^2 , R^3 , R^4 and A are as hereinbefore defined and one R^{1a} represents a group W
 wherein W is a halogen atom or a trifluoromethylsulfonyloxy group, or W is a group M
 selected from a boron derivative e.g. a boronic acid function $B(OH)_2$ or a metal function
 such as trialkylstannylyl e.g. $SnBu_3$, zinc halide or magnesium halide, and when q is 2 the
 other R^{1a} is R^1 ; with a compound Ar^3-W^1 , wherein W^1 is a halogen atom or a
 10 trifluoromethylsulfonyloxy group when W is a group M or W^1 is a group M when W is a
 halogen atom or a trifluoromethylsulfonyloxy group;

(d) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is O or S,
 reacting a compound of formula (V):

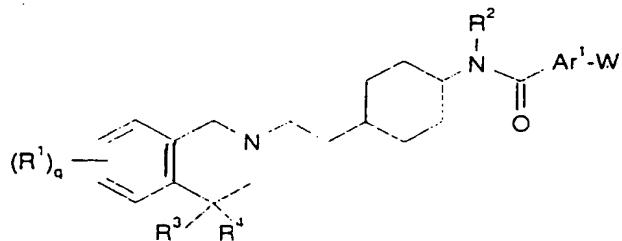


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Formula (V)

wherein R^2 , R^3 , R^4 and A are as hereinbefore defined and one R^{1b} represents a group
 ZH and when q is 2 the other R^{1b} represents R^1 ; with a reagent serving to introduce the
 20 group Ar^3 ;

(e) to prepare a compound of formula (I) where Y is a bond, reaction of a
 compound of formula (VI):



Formula (VI)

25

wherein R¹, R², R³, R⁴, Ar¹, W and q are as hereinbefore defined, with a compound Ar²-W¹, wherein W¹ is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M, or W¹ is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

- 5 (f) interconversion of one compound of formula (I) to a different compound of formula (I) e.g. (i) alkylation of a compound (I) wherein R² represents hydrogen, (ii) conversion of one R¹ from alkoxy (e.g. methoxy) to hydroxy, or (iii) conversion of R¹ from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv) conversion of a compound wherein Y represents S to a compound wherein Y is SO₂ or
- 10 (v) conversion of Y from CO to CH₂;
- (g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by conventional methods, e.g. chromatography or crystallisation; and optionally thereafter forming a salt of formula (I).

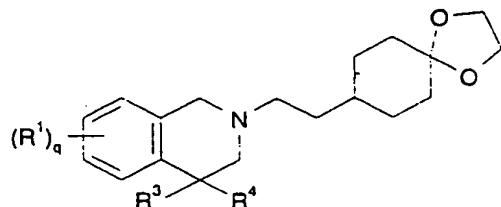
Process (a) may be effected using conventional methods for the formation of an amide bond. When X is the residue of an activated ester this may be formed with e.g. a carbodiimide such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The reaction may be carried out in a solvent such as dichloromethane.

Reaction of a compound of formula (IV) with Ar³W¹, according to process (c) or a compound of formula (VI) with Ar²-W¹ according to process (e) may be effected in the presence of a transition metal eg palladium catalyst such as *bis*-triphenylphosphinepalladium dichloride or *tetrakis*-triphenylphosphinepalladium (0). When M represents a boronic acid function such as B(OH)₂ the reaction may be carried out under basic conditions, for example using aqueous sodium carbonate in a suitable solvent such as dioxane. When M is trialkylstannyl the reaction may be carried out in an inert solvent, such as xylene or dioxane optionally in the presence of LiCl. When M is a zinc or magnesium halide the reaction may be effected in an aprotic solvent such as tetrahydrofuran. The substituent W is preferably a halogen atom such as bromine, or a sulfonyloxy group such as trifluoromethylsulfonyloxy; and W¹ is preferably a group M, such as trialkylstannyl or B(OH)₂.

In process (d) the reagent serving to introduce the group Ar³ is preferably a compound of formula Ar³-Hal, wherein Hal is a halogen atom. The reaction may be effected in the presence of a base, such as potassium carbonate, in a solvent such as dimethylformamide.

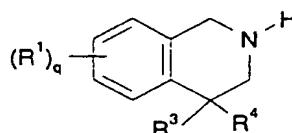
Interconversion reactions according to process (f) may be effected using methods well known in the art.

Compounds of formula (II) may be prepared by conversion of a compound of formula (VII), wherein R¹, R³, R⁴ and q are as hereinbefore defined.

**Formula (VII)**

into a corresponding ketone, followed by reductive amination. This may be effected by
5 methods well known in the art for (i) conversion of a ketal to a ketone in the presence of aqueous acid; followed by (ii) reductive amination of the ketone with R²NH₂ or ammonium acetate in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction
10 may conveniently be effected in a solvent such as methanol, ethanol or dichloroethane.

A compound of formula (VII) may itself be prepared by reacting a compound of formula (VIII):

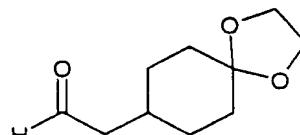


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Formula (VIII)

wherein R¹, R³, R⁴ and q are as hereinbefore defined;
with a compound of formula (IX):

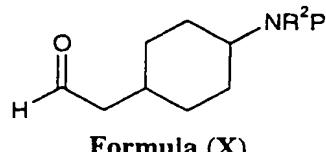
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**Formula (IX)**

in the presence of a reducing agent. Suitable reducing agents which may be employed
25 include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as ethanol or dichloroethane.

The individual *cis*- and *trans*- isomers of a compound of formula (II) may be prepared starting from *cis*- or *trans*- 4-amino-cyclohexaneacetic acid (T.P. Johnson, *et al.*,
30 J. Med. Chem., 1997, (20), 279-290) followed by functional group interchange and/or

protection using methods well known in the art, to give the individual *cis*- or *trans*-isomers of a compound of formula (X):



5

wherein R² is as hereinbefore defined, and P is a protecting group, for example trifluoroacetyl or *tert*-butoxycarbonyl. Subsequent reaction of a compound of formula (X) with a compound of formula (VIII) in the presence of a reducing agent as described above followed by deprotection using standard methodology gives the individual isomers of a compound of formula (II) wherein R² is as hereinbefore defined.

Compounds of formula (III) are known or may be prepared using standard procedures.

Compounds of formula (IV), (V) or (VI) may be prepared by processes analogous to (a), (b), (c) and (d) described above. Compounds Ar²W¹, Ar³W¹ and Ar³Hal are commercially available or may be prepared by standard methods. Compounds of formula (VIII) are known in the literature or may be prepared by known methods. The compound of formula (IX) is likewise known in the literature.

Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D₃ receptor, and are expected to be useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. Compounds of formula (I) have also been found to have greater affinity for dopamine D₃ than for D₂ receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D₂ receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the recently characterised dopamine D₃ receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993). Preferred compounds of the present invention are therefore those which have higher affinity for dopamine D₃ than dopamine D₂ receptors (such affinity can be measured using standard methodology for example using cloned dopamine receptors). Said compounds may advantageously be used as selective modulators of D₃ receptors.

The compounds of formula (I) are of potential use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders. Furthermore, they could have utility as adjunct therapy in Parkinson's Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (eg see Schwartz et al., Brain Res. Reviews, 1998, 26,

236-242). From the localisation of D₃ receptors, it could also be envisaged that the compounds could also have utility for the treatment of substance abuse where it has been suggested that D₃ receptors are involved (eg see Levant, 1997, Pharmacol. Rev., 49, 231-252). Examples of such substance abuse include alcohol, cocaine and nicotine abuse.

5 Other conditions which may be treated by the compounds include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety, cognitive impairment including memory disorders such as Alzheimers disease, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, 10 vertigo, dementia, circadian rhythm disorders and gastric motility disorders e.g. IBS.

In a further aspect therefore the present invention provides a method of treating conditions which require modulation of dopamine D₃ receptors, for example psychoses such as schizophrenia, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

15 The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine D₃ receptors, for example psychoses such as schizophrenia.

20 A preferred use for D₃ antagonists according to the present invention is in the treatment of psychoses such as schizophrenia.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound 25 of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

30 The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an 35 aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of 40 such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a

dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

The ability of the compounds to bind selectively to human D₃ dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [¹²⁵I] iodosulpride binding to human D₃

5 dopamine receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or
10 three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -40°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

15 **Preparation of CHO cell membranes**

Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 20mM EDTA, 0.2 M sucrose. The suspension was homogenised using an Ultra-Turrax at full speed for 15 sec. The homogenate was centrifuged at 18,000 r.p.m for 20 min at 4°C in a Sorvall RC5C
20 centrifuge. The membrane pellet was resuspended in ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), using an Ultra-Turrax, and re-centrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C. The membranes were washed two more times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C). The final pellet was resuspended in 50 mM Tris salts (pH 7.4 @ 37°C), and the protein content determined using bovine serum albumin as a standard
25 (Bradford, M. M. (1976) Anal. Biochem. 72, 248-254).

Binding experiments on cloned dopamine receptors

Crude cell membranes were incubated with 0.1 nM [¹²⁵I] iodosulpride (~2000 Ci/mmol; Amersham, U. K.), and the test compound in a buffer containing 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 0.1% (w/v) bovine serum albumin, in a total volume of 1 ml for 30 min at 37°C. Following incubation, samples were filtered using a Brandel Cell Harvester, and washed three times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂. The radioactivity on the filters was measured using a Cobra gamma counter
35 (Canberra Packard). Non-specific binding was defined as the radioligand binding remaining after incubation in the presence of 100 µM iodosulpride. For competition curves, 14 concentrations (half-log dilutions) of competing cold drug were used. Competition curves were analysed simultaneously whenever possible using non-linear least-squares fitting procedures, capable of fitting one, two or three site models.
40 Compounds of Examples tested according to this method had pKi values in the range 7.0 – 8.0 at the human cloned dopamine D₃ receptor.

Functional Activity at cloned dopamine receptors

The functional activity of compounds at human D₂ and human D₃ receptors (ie agonism or antagonism) may be determined using a Cytosensor Microphysiometer (McConnell HM et al Science 1992 257 1906-1912) In Microphysiometer experiments, cells (hD₂_CHO or hD₃_CHO) were seeded into 12mm Transwell inserts (Costar) at 300000 cells/cup in foetal calf serum (FCS)-containing medium. The cells were incubated for 6h at 37°C in 5%CO₂, before changing to FCS-free medium. After a further 16-18h, cups were loaded into the sensor chambers of the Cytosensor Microphysiometer (Molecular Devices) and the chambers perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl) at a flow rate of 100 ul/min. Each pump cycle lasted 90s. The pump was on for the first 60s and the acidification rate determined between 68 and 88s, using the Cytosoft programme. Test compounds were diluted in running medium. In experiments to determine agonist activity, cells were exposed (4.5 min for hD₂, 7.5 min for hD₃) to increasing concentrations of putative agonist at half hour intervals. Seven concentrations of the putative agonist were used. Peak acidification rate to each putative agonist concentration was determined and concentration-response curves fitted using Robofit [Tilford, N.S., Bowen, W.P. & Baxter, G.S. Br. J. Pharmacol. (1995) in press]. In experiments to determine antagonist potency, cells were treated at 30 min intervals with five pulses of a submaximal concentration of quinpirole (100 nM for hD₂ cells, 30 nM for hD₃ cells), before exposure to the lowest concentration of putative antagonist. At the end of the next 30 min interval, cells were pulsed again with quinpirole (in the continued presence of the antagonist) before exposure to the next highest antagonist concentration. In all, five concentrations of antagonist were used in each experiment. Peak acidification rate to each antagonist concentration was determined and concentration-inhibition curves fitted using Robofit.

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
35 Solvent/complexing agent	to 100 ml

Bolus Injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

40 Buffer : Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent : Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

Compound	1 - 40 mg
5 Diluent/Filler *	50 - 250 mg
Binder	5 - 25 mg
Disentegrant *	5 - 50 mg
Lubricant	1 - 5 mg
Cyclodextrin	1 - 100 mg

10

* may also include cyclodextrins

Diluent : e.g. Microcrystalline cellulose, lactose, starch

Binder : e.g. Polyvinylpyrrolidone, hydroxypropymethylcellulose

15 Disintegrand : e.g. Sodium starch glycollate, crospovidone

Lubricant : e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension

Compound	1 - 40 mg
20 Suspending Agent	0.1 - 10 mg
Diluent	20 - 60 mg
Preservative	0.01 - 1.0 mg
Buffer	to pH ca 5 - 8
Co-solvent	0 - 40 mg
25 Flavour	0.01 - 1.0 mg
Colourant	0.001 - 0.1 mg

Suspending agent : e.g. Xanthan gum, microcrystalline cellulose

Diluent : e.g. sorbitol solution, typically water

30 Preservative : e.g. sodium benzoate

Buffer : e.g. citrate

Co-solvent : e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

The invention is further illustrated by the following non-limiting examples :

35

Description 1

trans-2-(1-(4-(*N*-*tert*-Butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester

40 A mixture of *trans*-(4-amino)cyclohexylactic acid hydrogen sulfate (T.P. Johnston *et al*: J. Med Chem., 1977, 20 (2), 279-290), (27.0g, 106mmol), conc. H₂SO₄ (3ml), and

methanol (300ml) was stirred at reflux for 5h. Resulting solution was filtered and the filtrate evaporated *in vacuo* to give a brown oil (36g). A mixture of this material, triethylamine (36ml; 26.1g, 259 mmol), dichloromethane (600ml) and di-*t*-butyl dicarbonate (25.5g, 117mmol) was stirred at 20°C for 18h. Resulting solution was partitioned between saturated aqueous NaHCO₃ (500ml) and dichloromethane (3x200ml), and the combined extracts were dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound (24.6g, 86%) as a colourless solid.

5 ¹H NMR (CDCl₃) δ: 1.08 (4H, m), 1.43 (9H, s), 1.76 (3H, m), 2.00 (2H, m), 2.20 (2H, d, J = 7 Hz), 3.37 (1H, m), 3.66 (3H, s), 4.39 (1H, br s).

Description 2

trans-2-(1-(4-(*N*-*tert*-Butyloxycarbonyl)amino)cyclohexyl)acetaldehyde

10 To a stirred solution of *trans*-2-(1-(4-(*N*-*tert*-butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester (46.0g, 170 mmol) in dry toluene (920ml) at -78°C under argon was added a solution of di-isobutylaluminium hydride (1M; 285 ml; 285 mmol), dropwise over 0.5h. Resulting solution was stirred for a further 0.3h and quenched with a mixture 15 of methanol (28ml) in toluene (50ml) and then poured into saturated aqueous potassium sodium tartrate (1.2L). The resultant mixture was extracted with ether (4x1L). The combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo* to give a waxy 20 solid which was purified using silica gel, eluting with 10-50% ethyl acetate/hexane to give the title compound (21.77g, 53%) as a colourless solid.

25 ¹H NMR (CDCl₃) δ: 1.12 (4H, m), 1.44 (9H, s), 1.78 (3H, m), 2.00 (2H, m), 2.33 (2H, dd, J = 7, 2 Hz), 3.37 (1H, m), 4.40 (1H, m), 9.75 (1H, m).

Description 3

α, α - Dimethylphenylacetonitrile

30 Iodomethane (48g, 0.34 mol) was added dropwise, with ice cooling to a stirred mixture of phenylacetonitrile (10g, 0.085 mol), sodium hydroxide (13.6g, 0.34 mol), dimethyl sulfoxide (80 ml) and water (13.6 ml). The resultant mixture was stirred at ambient 35 temperature for 1 hour before being poured into water (500 ml). The mixture was extracted with diethyl ether (2 x 300 ml) and combined organics washed with water (3 x 100 ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford a colourless oil (12.42g, 100%).

40 ¹H NMR (CDCl₃) δ : 1.72 (6H, s), 7.20-7.55 (5H, m).

Description 4**2-Methyl-2-phenylpropylamine**

5 To a stirred suspension of lithium aluminium hydride (4.85g, 0.128 mol) in anhydrous diethyl ether (245 ml) at ambient temperature under argon was added a solution of α,α -dimethylphenylacetonitrile (12.4g, 0.085 mol) in anhydrous diethyl ether (105ml) dropwise over 0.5 hour. The resultant was heated at reflux for 3 hours, cooled to ambient temperature and treated with water (4.6 ml), 15% aqueous sodium hydroxide (4.6 ml) and
10 water (13.8 ml) dropwise sequentially. The mixture was stirred for 1.5 hours, filtered and the filtrate dried (Na_2SO_4) and treated with 1N hydrogen chloride in ether (100 ml). The precipitated solid was filtered and dried to afford the title compound as the hydrochloride salt (9.4g, 52%).
15 ^1H NMR (DMSO) δ : 1.36 (6H, s), 3.00 (2H, s), 7.15-7.45 (5H, m), 7.98 (3H, br s).

Description 5**4,4-Dimethyl-3,4-dihydroisoquinoline**

A mixture of 2-methyl-2-phenylpropylamine (7g, 0.047 mol) and 96% formic acid (11 ml) was slowly heated to 200°C and kept at this temperature for 1.25 hours during which time excess formic acid and water was allowed to distil. This mixture was added at
25 160°C to a mixture of polyphosphoric acid (51g) and phosphorous pentoxide (10.5g) that had previously been heated at 170-180°C for 1 hour. The resultant mixture was heated at 175°C for 2 hours, before being cooled slightly and poured into water (500ml) with stirring. The mixture was washed with ethyl acetate and the aqueous layer basified with 40% aqueous sodium hydroxide and extracted with dichloromethane (3 x 200 ml).
30 Combined halogenated organics were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a brown oil (5.95g, 79%).

Mass spectrum (API $^+$): Found 160 (MH^+). $\text{C}_{11}\text{H}_{13}\text{N}$ requires 159.

35 ^1H NMR (CDCl_3) δ : 1.24 (6H, s), 3.60 (2H, m), 7.20-7.50 (4H, m), 8.37 (1H, m).

Description 6**4,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline**

Sodium borohydride (2.66g, 0.0733 mol) was added portionwise to a stirred solution of 4,4-dimethyl-3,4-dihydroisoquinoline (5.9g, 0.037 mol) in ethanol (100ml) under argon.

The resultant was stirred at room temperature for 18 hours, water (400ml) carefully added and the mixture extracted with ethyl acetate (3 x 200ml). Combined extracts were washed with water and extracted into 5N hydrochloric acid (3 x 50ml). Combined acidic extracts were washed with ethyl acetate, basified with 40% aqueous sodium hydroxide and extracted into dichloromethane (3 x 100ml). Combined extracts were dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as an orange oil (4.15g, 70%).

Mass spectrum (API⁺): Found 162 (MH⁺). C₁₁H₁₅N requires 161.

10 ¹H NMR (CDCl₃) δ: 1.28 (6H, s), 2.87 (2H, s), 4.01 (2H s), 6.90-7.40 (4H, m)

15 **Description 7**
15 *trans*-2-(2-(1-(4-(N-tert-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

20 A mixture of *trans*-2-(1-(4-(N-tert-butyloxycarbonyl)amino)cyclohexyl)acetaldehyde (3.26g, 0.0135 mol), 4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (2.21g, 0.0137 mol) and sodium triacetoxyborohydride (4.31g, 0.0203 mol) in 1,2-dichloroethane (100ml) was stirred at room temperature for 3 hours. The resultant solution was partitioned between saturated sodium hydrogen carbonate (300 ml) and dichloromethane (100ml). The organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The residue was

25 chromatographed on silica gel using 0-20% ethyl acetate in hexane gradient elution to afford the title compound as a colourless oil (3.95g, 76%).

Mass spectrum (API⁺): Found 387 (MH⁺). C₂₄H₃₈N₂O₂. requires 356

30 ¹H NMR (CDCl₃) δ: 0.95-1.20 (4H, m), 1.20 - 1.35 (1H, br m), 1.29 (6H, s), 1.44 (9H, s), 1.40-1.55 (2H, m), 1.80 (2H, m), 1.98 (2H, m), 2.38 (2H, s), 2.45 (2H, t, J = 7Hz), 3.40 (1H, br m), 3.55 (2H, s), 4.35 (1H, m), 6.95-7.35 (4H, m).

35 **Description 8**
35 *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

40 A mixture of *trans*-2-(2-(1-(4-N-tert-butyloxycarbonyl)amino)cyclohexyl)ethyl)-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (3.9g 0.010 mol), trifluoroacetic acid (25ml) and dichloromethane (100ml) was stirred at 40°C for 0.5hour. The resultant solution was

evaporated *in vacuo* and the residue partitioned between water (200 ml) and ethyl acetate (200ml). The aqueous layer was basified with 2N sodium hydroxide and extracted into dichloromethane (3 x 100ml). Combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield the title compound as a colourless oil (2.52g, 88%).

5

Mass Spectrum (API $^+$): Found 287 (MH^+). $\text{C}_{19}\text{H}_{30}\text{N}_2$ requires 286

10 ^1H NMR (CDCl_3) δ : 0.80 - 1.20 (4H, m), 1.20 - 1.40 (1H, m), 1.29 (6H, m), 1.55 (4H, m), 1.70 - 1.95 (4H, m), 2.39 (2H, s), 2.46 (2H, t, $J = 8$ Hz), 2.59 (1H, m), 3.55 (2H, s), 6.90 - 7.35 (4H, m).

Description 9

15 **α,α -Dimethyl-(4-bromo)phenylacetonitrile**

Prepared from 4-bromophenylacetonitrile (15g, 0.0765 mol) using the method of description 3 as a pale orange-red oil (16.51g, 94%).

20 ^1H NMR (CDCl_3) δ : 1.71 (6H, m), 7.35 (2H, d, $J = 9$ Hz), 7.52 (2H, d, $J = 9$ Hz)

Description 10

25 **2-(4-Bromophenyl)-2-methylpropylamine**

Prepared from α,α -dimethyl-(4-bromo)phenylacetonitrile (16g, 0.0676 mol) using the method of description 4 to afford the title compound as the hydrochloride salt (16.87g, 89%).

30

^1H NMR (CDCl_3) δ : 1.23 (6H, s), 2.89 (2H, s), 7.27 (2H, d, $J = 9$ Hz), 7.43 (2H, d, $J = 9$ Hz), 7.77 (3H, br s).

35 **Description 11**

7-Bromo-4,4-dimethyl-3,4-dihydroisoquinoline

Prepared from 2-(4-bromophenyl)-2-methylpropylamine (8.32g, 0.0365 mol) using the method of description 5 as a colourless solid (3.7g, 43%).

Mass Spectrum (API $^+$): Found 238 (MH^+). $\text{C}_{11}\text{H}_{12}{^{79}\text{Br}}\text{N}$ requires 237.

¹H NMR (CDCl₃) δ: 1.22 (6H, s), 3.62 (2H, m), 7.23 (1H, d, J = 8Hz), 7.41 (1H, d, J = 2 Hz), 7.53 (1H, dd, J = 2, 8 Hz), 8.31 (1H, m).

5

Description 12

7-Bromo-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

10 Prepared from 7-bromo-4,4-dimethyl-3,4-dihydroisoquinoline (3.7g, 0.0155 mol) using the method of description 6 as a yellow oil (2.81g, 76%).

Mass spectrum (API⁺): Found 240 (MH⁺). C₁₁H₁₄⁷⁹BrN requires 239.

15 ¹H NMR (CDCl₃) δ: 1.24 (6H, s), 2.82 (2H, s), 3.96 (2H, s), 7.10-7.30 (3H, m).

Description 13

N-tert-Butyloxycarbonyl-7-bromo-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

20 Di-tert-butylcarbonate (2.99g, 0.0137 mol) in dichloromethane (10 ml) was added dropwise over 0.16 hours to a stirred solution of 7-bromo-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (3.0g, 0.0125 mol) and triethylamine (1.9ml, 0.0138 mol) in dichloromethane (40ml) at 0°C under argon. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed with water (100ml), 5% aqueous citric acid (2 x 50ml), brine (50ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as an orange oil (4.2g, 100%).

30 ¹H NMR (CDCl₃) δ *inter alia* 1.27 (6H, s), 1.88 (9H, s), 3.39 (2H, s) 4.59 (2H, s), 7.05 - 7.35 (3H, m).

Description 14

35

7-Cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

40 A mixture of N-tert-butyloxycarbonyl-7-bromo-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (4.2g, 0.01236 mol) and copper (I) cyanide (2.2g, 0.0247 mol) in N-methylpyrrolidinone (120ml) was heated at vigorous reflux for 2 hours. On cooling the mix was poured into 0.880 ammonia (300ml) and water (300ml) and extracted into ethyl acetate (4 x 200ml). Combined organic extracts were washed with 1:1 0.880

ammonia: water (3 x 150ml), water (3 x 200ml) and brine (150ml) and dried (Na_2SO_4). Solvent was removed *in vacuo* to afford the title compound as a pale brown solid (1.99g, 86%).

5 ^1H NMR (CDCl_3) δ *inter alia*: 1.28 (6H, s), 1.75 (1H, br s), 2.87 (2H, s), 4.01 (2H, s), 7.20-7.45 (3H, m).

Description 15

10 ***trans*-2-(2-(1-(4-(N-tert-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-7-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline**

15 Prepared from 7-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (1.8g, 0.01 mol) and *trans*-2-(1-(4-(N-tert-butylloxycarbonyl)amino)cyclohexyl)acetaldehyde (2.3g, 0.01 mol) using the method of description 7 as a pale yellow oil (1.65g, 40%).

Mass spectrum (API $^+$): Found 412 (MH^+). $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_2$ requires 411.

20 ^1H NMR (CDCl_3) δ : 0.95-1.20 (4H, m), 1.20-1.40 (1H, m), 1.29 (6H, s), 1.40-1.55 (2H, m), 1.44 (9H, s), 1.79 (2H, m), 1.98 (2H, m), 2.40 (2H, s), 2.48 (2H, t, $J=7\text{Hz}$), 3.36 (1H, br m), 3.56 (2H, s), 4.35 (1H, m), 7.20-7.50 (3H, m).

25 **Description 16**

***trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-7-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline**

30 Prepared from *trans*-2-(2-(1-(4-(N-tert-butylloxycarbonyl)amino)cyclohexyl)ethyl)-7-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (1.65g, 0.004 mol) by the method of description 8 as a pale green gum (1.05g, 85%)

Mass spectrum (API $^+$): Found 312 (MH^+). $\text{C}_{20}\text{H}_{29}\text{N}_3$ requires 311

35 ^1H NMR (CDCl_3) δ : 0.85-1.20 (4H, m), 1.29 (6H, s), 1.35-1.55 (5H, m), 1.65-1.90 (4H, m), 2.40 (2H, s), 2.51 (2H, t, $J=7\text{Hz}$), 2.60 (1H, m), 3.56 (2H, s), 7.20-7.45 (3H, m).

40 **Description 17**

α,α -Dimethyl-(3-methoxy)phenylacetonitrile

Prepared from 3-methoxyphenylacetonitrile (50g, 0.34 mol) using the method of description 3 as a yellow oil (58.7g, 99%).

5 ^1H NMR (CDCl_3) δ : 1.71 (6H, s), 3.82 (3H, s), 6.80 (1H, dd, $J = 2, 8$ Hz), 7.00 (2H, m),
7.30 (1H, m).

10 **Description 18**

15 **2-(3-Methoxyphenyl)-2-methylpropylamine**

Prepared from α, α -dimethyl-(3-methoxy)phenylacetonitrile (58.7g, 0.335 mol) using the method of description 4 to afford the title compound as the hydrochloride salt (56g, 78%).

15 ^1H NMR (DMSO d_6) δ : 1.34 (6H, s), 3.00 (2H, s), 3.76 (3H, s), 6.85 (1H, m), 6.95 (2H, m), 7.30 (1H, m), 7.90 (3H, br s).

20 **Description 19**

25 **4,4-Dimethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline**

A mixture of 2-(3-methoxyphenyl)-2-methylpropylamine (7.5g, 0.042 mol), 40% aqueous formaldehyde (3.2g, 0.043 mol) and water (3.2ml) was stirred at room temperature for 3 hours then heated on a steam bath for 0.5 hour. On cooling the mixture was partitioned between water (100ml) and dichloromethane (50ml) and the aqueous layer extracted with dichloromethane (3x50ml). Combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was mixed with water (3.6ml) and concentrated hydrochloric acid (5 ml) and heated on a steam bath under argon for 2 hours. On cooling, water (300ml) was added and the mixture washed with dichloromethane (2x50ml). The aqueous layer was basified with solid potassium carbonate and extracted into dichloromethane (3x75ml). Combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a pale yellow oil (6.5g, 85%).

35 Mass spectrum (API $^+$): Found 192 (MH^+) $\text{C}_{12}\text{H}_{17}\text{NO}$ requires 191.

40 ^1H NMR (CDCl_3) δ : 1.21 (6H, s), 1.76 (1H, br s), 2.80 (2H, s), 3.78 (3H, s), 3.95 (2H, s), 6.65 (1H, dd, $J=2, 8$ Hz), 6.75-6.95 (2H, m).

45 **Description 20**

4,4-Dimethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline

A mixture of 4,4-dimethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (23.9g, 0.125 mol) and 48% aqueous hydrobromic acid (158ml) were heated at vigorous reflux for 4 hours.

5 The reaction mixture was cooled and evaporated *in vacuo*. The residue was triturated with diethyl ether (20ml), 1:1 diethyl ether:thf (20ml) and diethyl ether (3x20ml) and dried *in vacuo* to afford the title compound as the hydrobromide salt (17.5g, 53%).

Mass spectrum (API⁺): Found 178(MH⁺). C₁₁H₁₅NO requires 177

10 ¹H NMR (DMSO d₆) δ: 1.31 (6H, s), 3.20 (2H, s), 4.15 (2H, s), 6.70 (1H, dd, J=2,8Hz), 6.80 (1H,d, J=2Hz), 6.95 (1H, d, J=8Hz) 8.90 (2H, br s), 9.40 (1H, br s).

15 **Description 21**

N-tert-Butyloxycarbonyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

20 A mixture of 4,4-dimethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (25.5g, 0.0988 mol), di-tert-butyl dicarbonate (22.15g, 0.101 mol), triethylamine (15.48ml, 0.111 mol), water (56ml) and tetrahydrofuran (176ml) were stirred at room temperature for 2 hours. The mixture was concentrated to approximately 50ml *in vacuo* and partitioned between dichloromethane (500 ml) and water (500ml). The organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The residue was dissolved in

25 dichloromethane (250ml), triethylamine (21ml, 0.151 mol) added, stirred and cooled to 5°C and trifluoromethane sulfonic anhydride (23ml, 0.136mol) added at such a rate so that the temperature remained below 10°C. One complete addition the mixture was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was

30 partitioned between dichloromethane and saturated sodium hydrogen carbonate (250ml). The aqueous layer was further extracted with dichloromethane (3x100ml). Combined organics were washed with water (250ml), brine (250ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was chromatographed on silica gel (500g) using 0-10% ethyl acetate in hexane gradient elution to afford the title compound as a yellow oil (40g, 99%).

35 ¹H NMR (CDCl₃) δ : 1.26 (6H, s), 1.49 (9H, s), 3.42 (2H, s), 4.63 (2H, s), 6.90-7.20 (3H, m).

40

Description 22**N-tert-Butyloxycarbonyl-6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline**

Tetrakis (triphenylphosphine)palladium (0) (4.10g, 0.0035 mol) was added to a suspension of N-tert-butyloxycarbonyl-4,4-dimethyl-6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline (36.37g, 0.089 mol) and zinc cyanide (10.44g, 0.089 mol) in anhydrous dimethyl formamide (280ml) under argon. The resultant was heated at 100°C for 4 hours, cooled and poured into water (800ml). The mixture was filtered through kieselguhr and the filter cake washed with ethyl acetate. The bilayered filtrate was separated and the aqueous layer extracted into ethyl acetate (4x500ml). Combined organics were washed with water (3x250ml), brine (250ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel using 0-15% ethyl acetate in hexane gradient elution to afford the title compound as a colourless oil (21.75g, 85%).

^1H NMR (CDCl_3) δ : 1.28 (6H, s), 1.50 (9H, s), 3.40 (2H, s), 4.65 (2H, s), 7.15 (1H, d, J=8Hz) 7.43 (1H, dd, J=8Hz), 7.70 (1H, m).

Description 23

20 **6-Cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline**

Prepared from N-tert-butyloxycarbonyl-6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (21.75g, 0.076 mol) using the method of description 8 (13.84g, 98%).

25 ^1H NMR (CDCl_3) δ : 1.28 (6H, s), 1.80 (1H, s), 2.86 (2H, s), 4.04 (2H, s), 7.05 (1H, d, J=8Hz), 7.40 (1H, dd, J=2, 8Hz), 7.60 (1H, d, J=2Hz)

30 **Description 24**

trans-2-(2-(1-(4-(N-tert-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline

35 Prepared from 6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (5.44g, 0.0292 mol) and *trans*-2-(1-(4-(N-tert-butyloxycarbonyl)amino)cyclohexyl)acetaldehyde (7.05g, 0.0292 mol) using the method of description 7 as a colourless oil (13g) which was used without further purification.

40 Mass spectrum (API $^+$): Found 412 (MH^+). $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_2$ requires 411

¹H NMR (CDCl₃) δ: 0.9-1.15 (4H, m), 1.2-1.35 (1H, m), 1.29 (6H, s), 1.35-1.55 (2H, m), 1.44 (9H, s), 1.75 (2H, m), 1.97 (2H, m), 2.39 (2H, s), 2.47 (2H, t, J=7Hz), 3.36 (1H, m), 3.66 (2H, s), 4.35 (1H, m), 7.07 (1H, d, J=8Hz), 7.36 (1H, dd, J=2,8Hz), 7.58 (1H, d, J=2Hz).

5

Description 25

10 **trans-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline**

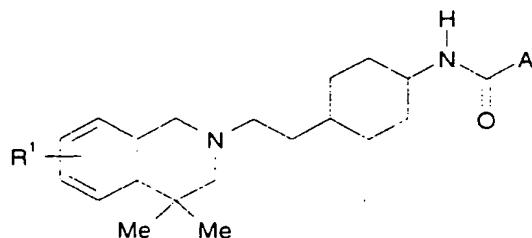
15 Prepared from *trans*-2-(2-(1-(4-N-tert-butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (total material as prepared in description 22) using the method of description 8 as a colourless solid (10g) which was used without further purification.

20

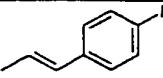
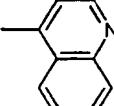
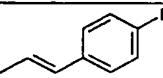
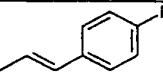
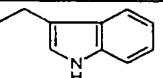
The Compounds of Examples tabulated below were all prepared using the following general method:-

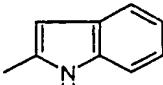
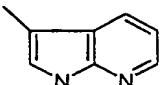
25 A mixture of the appropriate *trans*-2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (0.35 mmol), the appropriate acid (0.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.35 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (5ml) was shaken for 16h. Saturated sodium bicarbonate (4ml) was then added and the mixture shaken for 0.25h.

30 Chromatography of the organic layer on silica with 50 - 100% ethyl acetate in hexane and 0 - 10% methanol in ethyl acetate gradient elution gave the title compounds.



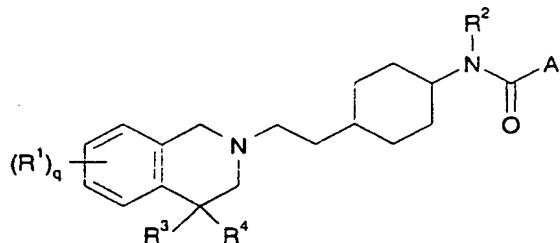
Example No.	R¹	A	Mass Spectrum (API ⁺)	¹ H NMR (CDCl ₃ unless stated)

1	6-CN		460 ; C ₂₉ H ₃₄ FN ₃ O requires 459	1.0-1.55 (7H, m), 1.30 (6H, s), 1.83 (2H, m), 2.05 (2H, m), 2.41 (2H, s), 2.49 (2H, t, J = 6 Hz), 3.60 (2H, s), 3.86 (1H, m), 5.42 (1H, d, J = 8 Hz), 6.26 (1H, d, J = 16 Hz), 6.95-7.15 (3H, m), 7.37 (1H, dd, J = 2, 8 Hz), 7.47 (2H, m), 7.56 (1H, d, J = 16 Hz), 7.59 (1H, s).
2	6-CN		467; C ₃₀ H ₃₄ N ₄ O requires 466	1.10-1.40 (5H, m), 1.31 (6H, s), 1.48 (2H, m), 1.88 (2H, m), 2.20 (2H, m), 2.35-2.55 (4H, m), 3.63 (2H, s), 4.08 (1H, m), 5.92 (1H, d, J = 8 Hz), 7.09 (1H, d, J = 8 Hz) 7.30-7.45 (2H, m), 7.50-7.65 (2H, m), 7.76 (1H, m), 8.13 (1H, d, J = 8 Hz), 8.19 (1H, d, J = 8 Hz), 8.91 (1H, d, J = 4 Hz).
3	7-CN		460 ; C ₂₉ H ₃₄ FN ₃ O requires 459	1.05-1.20 (5H, m), 1.30 (6H, s), 1.45 (2H, m), 1.83 (2H, m), 2.02 (2H, m), 2.41 (2H, s), 2.49 (2H, t, J = 7 Hz), 3.56 (2H, s), 3.85 (1H, m), 5.43 (1H, d, J = 8 Hz), 6.26 (1H, d, J = 16 Hz), 7.04 (2H, m), 7.30 (1H, s), 7.32-7.50 (4H, m), 7.56 (1H, d, J = 16 Hz).
4	H		435 ; C ₂₈ H ₃₅ FN ₂ O requires 434	1.05-1.20 (5H, m), 1.30 (6H, s), 1.48 (2H, m), 1.83 (2H, m), 2.04 (2H, m), 2.40 (2H, s), 2.47 (2H, t, J = 7 Hz), 3.56 (2H, s), 3.86 (1H, m), 5.42 (1H, d, J = 8 Hz), 6.26 (1H, d, J = 16 Hz), 6.90-7.25 (5H, m), 7.30 (1H, m), 7.46 (2H, m), 7.56 (1H, d, J = 16 Hz).
5	H		444 ; C ₂₉ H ₃₇ N ₃ O requires 443	0.75-1.25 (5H, m), 1.26 (6H, s), 1.43 (2H, m), 1.60-1.90 (4H, m), 2.35 (2H, s), 2.41 (2H, t, J = 7 Hz), 3.52 (2H, s), 3.60-3.85 (1H, m), 3.71 (2H, s), 5.47 (1H, d, J = 8 Hz), 7.53 (1H, d, J = 8 Hz), 6.97 (1H, d,

				$J = 7$ Hz), 7.00-7.35 (6H, m), 7.39 (1H, d, $J = 8$ Hz), 7.53 (1H, d, $J = 8$ Hz), 8.27 (1H, br s).
6	H		430; $C_{28}H_{35}N_3O$ requires 429	(DMSO) 1.00-1.25 (3H, m), 1.30 (6H, s), 1.32-1.60 (4H, m), 1.80-2.00 (4H, m), 2.42 (2H, s), 2.51 (2H, m), 3.56 (2H, s), 3.70-3.90 (1H, m), 6.95-7.30 (6H, m), 7.37 (1H, d, $J = 8$ Hz), 7.46 (1H, d, $J = 8$ Hz), 7.63 (1H, d, $J = 8$ Hz), 8.23 (1H, d, $J = 8$ Hz), 11.55 (1H, br s).
7	H		431 ; $C_{27}H_{34}N_4O$ requires 430	1.12 (6H, s), 1.15-1.40 (5H, m), 1.45 (2H, m), 1.85 (2H, m), 2.15 (2H, m), 2.56 (2H, m), 2.70 (2H, s), 3.76 (2H, s), 3.85-4.05 (1H, m), 5.73 (1H, d, $J = 8$ Hz), 6.95 - 7.15 (4H, m), 7.23 (1H, dd, $J = 5, 8$ Hz), 7.83 (1H, s), 8.30-8.45 (2H, m), 11.59 (1H, br s).

Claims :

1. A compound of formula (I) :



5 **Formula (I)**

wherein:

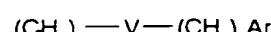
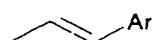
R¹ represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁-4alkyl, C₁-4alkoxy, arylC₁-4alkoxy, C₁-4alkylthio, C₁-4alkoxyC₁-4alkyl, C₃-6azacycloalkylC₁-4alkoxy, C₁-4alkanoyl, C₁-4alkoxycarbonyl, C₁-4alkylsulfonyl, C₁-4alkylsulfonyloxy, C₁-4alkylsulfonylC₁-4alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁-4alkyl, C₁-4alkylsulfonamido, C₁-4alkylamido, C₁-4alkylsulfonamidoC₁-4alkyl, C₁-4alkylamidoC₁-4alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁-4alkyl, arylcarboxamidoC₁-4alkyl, aroyl, aroylC₁-4alkyl, or arylC₁-4alkanoyl group; a group R⁵OCO(CH₂)_p, R⁵CON(R⁶)(CH₂)_p, R⁵R⁶NCO(CH₂)_p or R⁵R⁶NSO₂(CH₂)_p where each of R⁵ and R⁶ independently represents a hydrogen atom or a C₁-4alkyl group or R⁵R⁶ forms part of a C₃-6azacycloalkane or C₃-6(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar³-Z, wherein Ar³ represents an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring and Z represents a bond, O, S, or CH₂;

10 R² represents a hydrogen atom or a C₁-4alkyl group;

15 R³ and R⁴ each independently represent a C₁-4 alkyl group

q is 1 or 2;

20 A represents a group of the formula (a), (b), (c) or (d):



(a)

(b)

(c)

(d)

wherein

30 Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system:

Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring; and

5 Y represents a bond, $-\text{NHCO}-$, $-\text{CONH}-$, $-\text{CH}_2-$, or $-(\text{CH}_2)_m \text{Y}^1(\text{CH}_2)_n-$, wherein Y^1 represents O, S, SO_2 , or CO and m and n each represent zero or 1 such that the sum of $m+n$ is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;

10 r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4;

10 V represents a bond, O or S;
and salts thereof.

2. A compound according to claim 1 wherein q represents 1.

15 3. A compound according to any of the preceding claims wherein rings Ar, Ar^1 , or Ar^2 are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

20 4. A compound of formula (I) which is:
 $\text{trans-}(E)\text{-6-Cyano-4,4-dimethyl-2-[2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;

25 $\text{trans-6-Cyano-4,4-dimethyl-2-[2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;

$\text{trans-}(E)\text{-7-Cyano-4,4-dimethyl-2-[2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;

$\text{trans-}(E)\text{-4,4-dimethyl-2-[2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;

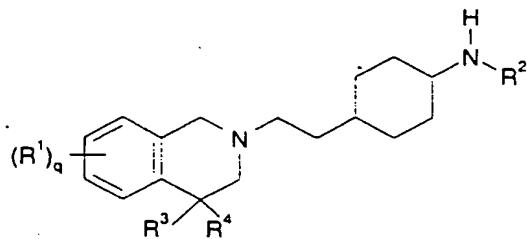
30 $\text{trans-4,4-dimethyl-2-[2-(1-(4-(3-indolyl)acetylamido)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;

$\text{trans-4,4-dimethyl-2-[2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;

35 $\text{trans-4,4-dimethyl-2-[2-(1-(4-(3-pyrrolo[2,3-b]pyridyl)carboxamido)cyclohexyl)ethyl]-1,2,3,4-tetrahydroisoquinoline}$;
or a salt thereof.

40 5. A process for preparing compounds of formula (I) which process comprises :

 (a) reacting a compound of formula(II):



5 wherein R¹, R², R³, R⁴ and q are as hereinbefore defined,
with a compound of formula (III):

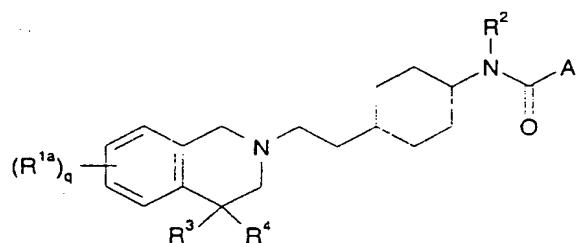
A-COX

Formula (III)

10 wherein A is as hereinbefore defined and X is a halogen atom or the residue of an activated ester;

15 (b) to prepare a compound of formula (I) by reacting a compound of formula (II) with a compound A-Br, or A-I, or A-OSO₂CF₃ in the presence of carbon monoxide and a catalyst;

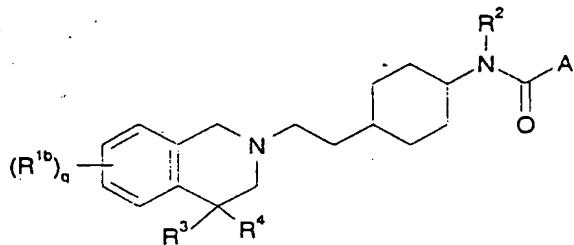
15 (c) to prepare a compound of formula (I) wherein R¹ is Ar³-Z and Z is a bond, reacting a compound of formula (IV):



Formula (IV)

20 wherein A, R², R³, R⁴ and q are as hereinbefore defined. one R^{1a} represents a group W wherein W is a halogen atom or a trifluoromethylsulfonyloxy group, or W is a group M selected from a boron derivative or a metal function. and when q is 2 the other R^{1a} is R¹; with a compound Ar³-W¹, wherein W¹ is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M or W¹ is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group;

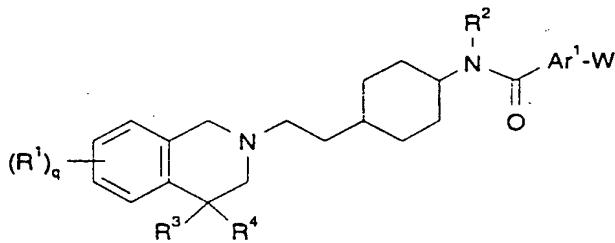
25 (d) to prepare a compound of formula (I) wherein R¹ is Ar³-Z and Z is O or S, reacting a compound of formula (V):



Formula (V)

5 wherein A, R², R³, R⁴ and q are as hereinbefore defined, one R^{1b} represents a group ZH and when q is 2 the other R^{1b} represents R¹; with a reagent serving to introduce the group Ar³;

(e) to prepare a compound of formula (I) where Y is a bond, reaction of a compound of formula (VI):



Formula (VI)

10

wherein R¹, R², R³, R⁴, q, Ar¹ and W are as hereinbefore defined, with a compound Ar²-W¹, wherein W¹ is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M, or W¹ is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

(f) interconversion of one compound of formula (I) to a different compound of formula (I) e.g. (i) alkylation of a compound (I) wherein R^2 represents hydrogen, (ii) conversion of one R^1 from alkoxy (e.g. methoxy) to hydroxy, or (iii) conversion of R^1 from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv) conversion of a compound wherein Y represents S to a compound wherein Y is SO_2 or (v) conversion of Y from CO to CH_2 ;

(g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by conventional methods; and optionally thereafter forming a salt of formula (I).

25

6. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of claims 1 to 7 or a physiologically acceptable salt thereof and a physiologically acceptable carrier therefor.

7. The use of a compound of formula (I) as claimed in any of claims 1 to 6 or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

5 8. Use according to claim 7 wherein the dopamine receptor is a dopamine D₃ receptor.

10 9. Use according to claim 7 or claim 8 wherein a dopamine antagonist is required.

10 10. Use according to any of claims 7 to 9 wherein the condition is a psychotic condition.

15 11. Use according to claim 10 wherein the psychotic condition is schizophrenia.

20 12. A method of treating a condition which requires modulation of a dopamine receptor which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in claim 1 or a physiologically acceptable salt thereof.